

A single-center, open, single-arm clinical study on the application of ursodeoxycholic acid for the prevention of novel coronavirus infections

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Confidentiality Statement

This document is confidential information of the Hospital of Hematology, Chinese Academy of Medical Sciences (Institute of Hematology, Chinese Academy of Medical Sciences) and is intended for the purpose of this clinical study only. It may not be disclosed to anyone other than the participants in the study and members of the Institutional Review Board. This information may not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of the Hospital of Hematology, Chinese Academy of Medical Sciences (Institute of Hematology, Chinese Academy of Medical Sciences).

Researcher Statement

I have familiarized myself with the protocol of this study and confirm that it contains the necessary elements for the implementation of the study and that the responsibilities related to this study protocol are clear. I agree to perform the relevant duties in accordance with Chinese laws and regulations, the Declaration of Helsinki, the Code of Quality Management for Drug Clinical Trials, and this study protocol, and to carry out the procedures specified in this study only after the Ethics Committee has approved the protocol and the subjects have given their informed consent. If modifications to the protocol are required, the modified protocol will be approved by the Ethics Committee before implementation, unless measures are necessary to protect the safety, rights, and interests of the subjects. I understand and comply with the requirements for the maintenance of original data.

Principal Investigator

Date

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1 ABSTRACT

Title: A single-center, open, single-arm clinical study on the application of ursodeoxycholic acid for the prevention of novel coronavirus infections
Planned research time: Expected to enroll healthy volunteers for 3 weeks and follow up for 8 weeks
Purpose of the study: 1) Primary research objectives Evaluation of the efficacy and safety of ursodeoxycholic acid in blocking the transmission of infectious novel coronaviruses in a population of medical workers 2) Secondary Research Objectives Exploring the evaluation of conversion to severe disease in people infected with novel coronavirus Exploring the evaluation of the persistence and reduction of symptoms in people infected with novel coronavirus Exploring the evaluation of antibody profiles in healthy volunteer populations Observing the safety of ursodeoxycholic acid drugs Evaluating the changes of S protein-specific T/B cell immunity before and after BF.7 infection after immunization with Wuhan Strain vaccine.
Study population: Healthy volunteers for this study were from medical workers (doctors, nurses, medical technicians, administrative logistics, medical students) who were not infected with novel coronavirus
Planned enrollment (sample size): The study is expected to enroll 130 healthy volunteers
Study Design Overview: This study is a single-center, open-ended, single-arm clinical study
Inclusion Criteria: Healthy volunteers suitable for enrollment in this study must meet all of the following criteria : 1) Age 18-65 years old 2) No restriction on gender 3) Medical-related personnel (working hours >20 hours per week) serving during the COVID-19 outbreak, including physicians, nurses, medical technicians, administrators, and medical students 4) COVID-19 nucleic acid test negative within 48 hours 5) Sign the informed consent form
Exclusion Criteria: Anyone who meets any of the following criteria shall not be selected for this study :

- 1) Exhibit COVID-19 symptoms, including fever, muscle pain, headache, cough, sore throat, and loss of smell and taste
- 2) Previous infection with novel coronavirus within 6 months
- 3) Previous (past 30 days), current or planned (during the study period) use of immunomodulatory-related drugs
- 4) Those with allergy or intolerance to ursodeoxycholic acid, gallbladder or bile duct disease, severe liver failure, or liver function impairment
- 5) Pregnancy and lactation
- 6) Use of drugs with which ursodeoxycholic acid is contraindicated
- 7) Other reported health conditions that make participation in the study not in the best interest of the individual

Shedding and exit criteria

- 1) Healthy volunteers request to withdraw from the study on their own
- 2) Female healthy volunteers planning to become pregnant or pregnant during the trial
- 3) Missed visits due to various reasons
- 4) In the judgment of the investigator, treatment should be discontinued from this protocol

Rejection Criteria:

- 1) Poor compliance with the requirements of the study and failure to follow the study plan
- 2) Those who received prophylactic drugs other than this drug during the trial

Research drug delivery protocols:

Drug name (specification formulation): ursodeoxycholic acid capsules.

Mode of administration/regimen: 250 mg/capsule, 2 capsules per day, for 4 weeks.

Duration of follow-up visits:

Dosing period:

Healthy volunteers took ursodeoxycholic acid capsules daily for 4 weeks from the date of enrollment

Follow-up period:

Healthy volunteers will be followed up once a week for a total of 8 weeks in case of new coronavirus infection.

Research Indicators:

- 1) Primary research indicators
Prevalence of novel coronavirus infection in healthy volunteers receiving 4 weeks of continuous ursodeoxycholic acid plus conventional protection during the study period.
- 2) Secondary Research Metrics
 - 1) The proportion of people infected with novel coronavirus who turned severe.
 - 2) the number of days that symptoms of a novel coronavirus infection such as fever, sore throat, headache, and muscle aches persisted in the population infected with novel coronavirus, and the number of days that the nucleic acid/antigen turned negative.
 - 3) The rate of positive serological antibodies in the population of healthy volunteers.
 - 4) The incidence of adverse events.

5) The difference of T/B lymphocyte specific response to Wuhan Strain and BF.7 Strain in different volunteers.

Safety evaluation:

Observe and record any adverse events that occur in healthy volunteers during the clinical study, including abnormal clinical symptoms and vital signs, abnormalities in laboratory tests, record the characteristics of clinical manifestations, severity, time of occurrence, duration, management and prognosis, and determine their correlation with the trial drug/treatment regimen, and evaluate safety according to NCI CTCAE version 5.0 standards

Statistical Methods:

SAS 9.4 software was used for statistical analysis of the data in this study, with continuous variables described by mean \pm standard deviation (Mean \pm SD) or median, maximum, minimum, and interquartile range (Median, Max, Min, IQR) and categorical variables described by rate or percentage. Comparisons of measurement data were performed by t-test/ANOVA or nonparametric test; comparisons of count data were performed by χ^2 test or Fisher's exact probability test. If not otherwise specified, all tests were performed as two-sided tests with a test level of $\alpha=0.05$.

2 Research Background

Researchers at the University of Cambridge, UK, and other institutions have found that ursodeoxycholic acid (UDCA) is able to turn off the ACE2 receptor, thereby blocking viral entry into human cells, and since the SARS-CoV from 2003 to the SARS-CoV-2 spectrum in 2019 utilizes ACE2 as the primary invasion receptor, even if subsequent SARS-CoV-2s continue to show new small variants, the drug maintains its effect. The study was published in Nature on December 5, 2022, entitled "FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2" [1]. Ursodeoxycholic acid (UDCA) was found to downregulate angiotensin-converting enzyme 2 (ACE2) expression by inhibiting the transcription factor FXR, thereby shutting down the entry of neocoronavirus into human cells. Since the drug acts on the host cell and not on the virus itself, it may be able to prevent current neo-coronavirus infections and should also be able to prevent future neo-coronavirus new mutants, as well as infections by other coronaviruses that utilize ACE2. Currently, China is in a period of high prevalence of neo-coronavirus infections, and there is an urgent need for clinical studies on prophylactic drugs

3 Research objectives

The purpose of this study is to evaluate whether ursodeoxycholic acid is an effective prophylactic agent against novel coronavirus (SARS-CoV-2) infection in medical personnel

3.1 Primary research objectives

Evaluation of the effectiveness and safety of ursodeoxycholic acid in blocking the transmission of infectious novel coronaviruses in adult populations

3.2 Secondary research objectives

- 1) To explore the evaluation of the transition to severe disease in the population infected with novel coronavirus;
- 2) To explore the evaluation of the persistence and reduction of symptoms in people infected with novel coronavirus;
- 3) To explore the evaluation of antibodies in a population of healthy volunteers;
- 4) To observe the safety of ursodeoxycholic acid drugs;
- 5) To evaluating the changes of S protein-specific T/B cell immunity before and after BF.7 infection after immunization with Wuhan Strain vaccine.

4 Study design

This is a single-center, open-ended, single-arm clinical study to evaluate the effectiveness of daily ursodeoxycholic acid plus routine protective measures for the prevention of novel coronavirus infection. The target sample size is 130 medical workers and each healthy volunteer will be followed weekly for nucleic acid/antigen testing or disease progression over an 8-week period for new crown infections.

5 Study population

Healthy volunteers for this study were drawn from medical workers who were not infected with novel coronavirus

5.1 Inclusion criteria

Healthy volunteers suitable for enrollment in this study must meet all of the following criteria:

- 1) Age 18 - 65 years old.
- 2) No restriction on gender.
- 3) Medical-related personnel (working hours >20 hours per week) serving during the COVID-19 outbreak, including physicians, nurses, medical technicians, administrators, and medical students
- 4) COVID-19 nucleic acid test negative within 48 hours
- 5) Sign the informed consent form

5.2 Exclusion Criteria

Anyone who meets any of the following criteria shall not be selected for this studies:

- 1) Exhibit COVID-19 symptoms, including fever, muscle pain, headache, cough, sore throat, and loss of smell and taste
- 2) Previous infection with novel coronavirus within 6 months
- 3) Previous (past 30 days), current or planned (during the study period) use of immunomodulatory-related drugs
- 4) Those with allergy or intolerance to ursodeoxycholic acid, gallbladder or bile duct disease, severe liver failure, or liver function impairment
- 5) Pregnancy and lactation
- 6) Use of drugs with which ursodeoxycholic acid is contraindicated

- 7) Other reported health conditions that make participation in the study not in the best interest of the individual

5.3 Off study criteria

Volunteers withdrew from the study for any of the following reasons.

- 1) A healthy volunteer's own request to withdraw from the study.
- 2) planned pregnancy or pregnancy during the trial in female healthy volunteers.
- 3) Loss of visit for various reasons.
- 4) The investigator's judgment should discontinue treatment in this protocol.

Healthy volunteers may withdraw their informed consent if they do not wish to continue to participate in the study. If a healthy volunteer decides to withdraw from the study, the investigator must be notified in a timely manner. The reason for withdrawal from the study should be documented, including the date and reason for withdrawal from the study.

5.4 Rejection Criteria

Volunteers were required to be excluded from the study for the following conditions

- 1) Those who are poorly compliant with the requirements of the study and fail to follow the study plan.
- 2) Those who receive prophylactic medications other than this drug during the trial.

6 Drug delivery measures

Drug Name (Specification Formulation).

Ursodeoxycholic acid capsule, 250mg/capsule.

6.1 Drug delivery method/protocol

Take two capsules orally with a meal, once daily

7 Visiting Arrangements

7.1 Screening Period

- Baseline Collection
 - 1) Basic demographic information such as age and sex.
 - 2) Type of neo-coronavirus vaccination and number of vaccinations received.
 - 3) novel coronavirus infection status of family members/personnel living with them.
 - 4) Personnel positions: e.g., physicians, nurses, medical technology, administrative logistics, medical students, etc.

- 5) Working department.
- 6) underlying disease status: e.g. hypertension, diabetes, cardiovascular disease, etc.
- 7) Combined medication use and drug allergy history.

- Routine Inspection:

- 1) Vital signs (heart rate, respiration, body temperature, etc.

- Retention of serum samples:

1) 5mL of blood was collected from healthy volunteers, of which 2mL of whole blood was directly frozen and the rest was extracted from the serum for freezing and storage.

- 2) Biological sample processing and storage.

Blood samples will be collected according to the follow-up plan, and the processing and storage will be carried out by the Biosample Bank of the Hospital of Blood Diseases, Chinese Academy of Medical Sciences. It will be managed in strict accordance with biosafety law, regulations on human genetic resources management and other relevant regulations.

7.2 Dosing period (4 weeks)

1) weekly nucleic acid testing (in lieu of nucleic acid results if positive for self-test antigens)

- 2) Weekly telephone follow-up for adverse events.

3) 5mL of blood is collected from healthy volunteers at the end of dosing or in case of infection during the period, of which 2mL of whole blood is directly frozen and the rest is extracted from the serum for freezing.

7.3 Follow-up period (8 weeks)

1) If a healthy volunteer develops novel coronavirus symptoms during the follow-up period, the volunteer's symptoms will be scored and recorded according to Table 1.

Table 1: New crown symptom assessment form

Symptoms	Rating			Score
	Slight =1	Medium =2	Serious =3	
Abdominal pain				
fatigue				
Cough				
Shortness of breath				
Diarrhea				
Muscle pain				
Headaches				
Taste and smell disorder				

Other				
Total Score				

- 1) Weekly telephone follow-up of AE status of healthy volunteers.
- 2) Detection of antibodies before and after drug administration.
- 3) Weekly monitoring of nucleic acid/antigen status of new crowns in healthy volunteers during the study period, and testing for nucleic acid at any time during the study period when volunteers develop symptoms of novel coronavirus (in case of positive self-test antigen, this can be substituted for nucleic acid results)./
- 4) Blood will be collected for freezing and storage in case of infection and out of the group.

Table 2: Table of observation items during the visit

	Baseline period	Detection frequency	In case of infection
Demographic Information	√		
Nucleic acid testing	√	Weekly	√
Vital signs	√		
AE Telephone follow-up AE	√	Weekly	
Blood collection for freezing and storage	√	Week 4 and 8	

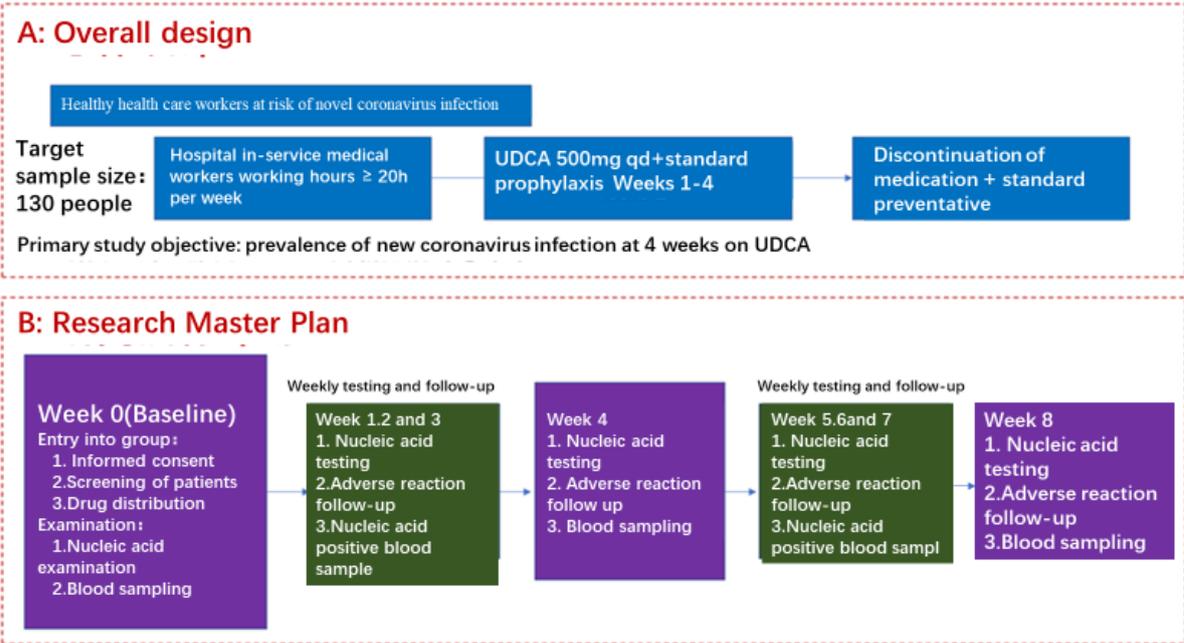


Figure 1: Research flow chart

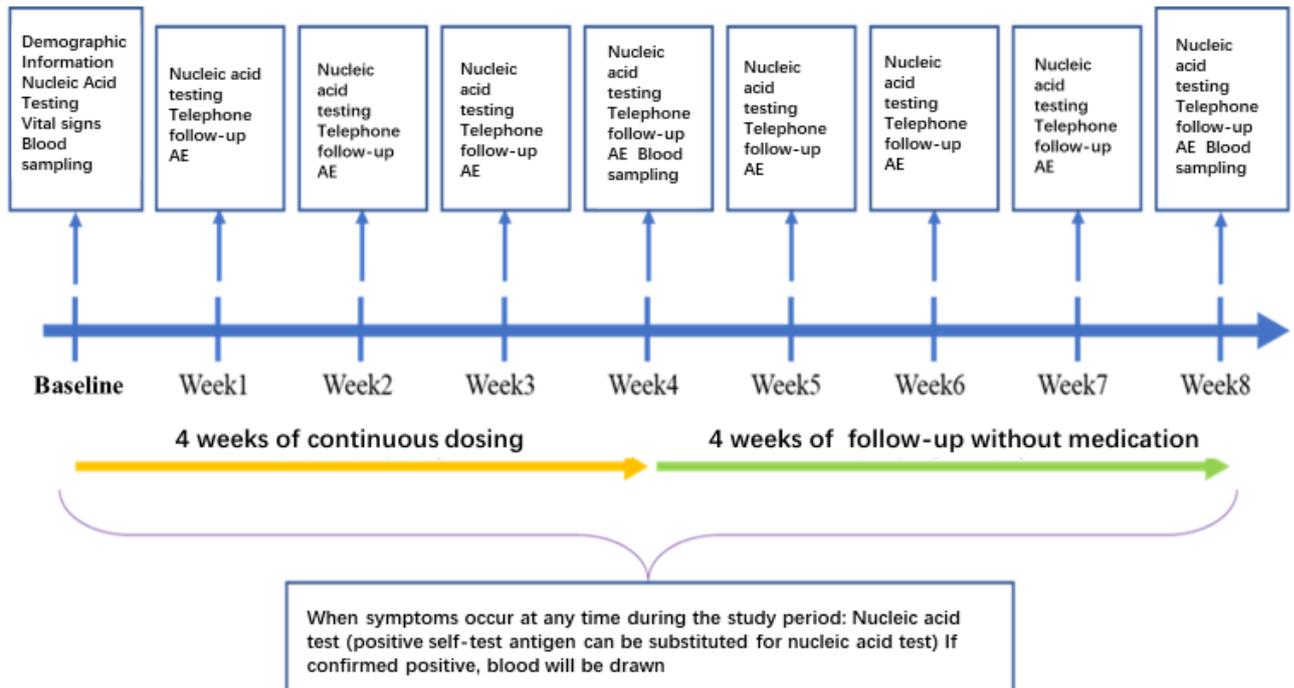


Figure 2: Flow chart of the visit

8 Research indicators

8.1 Primary research indicators

Prevalence of novel coronavirus infection in healthy volunteers receiving 4 weeks of continuous ursodeoxycholic acid plus conventional protection during the study period, the proportion of healthy volunteers infected with novel coronavirus during the study period as a percentage of the study population

8.2 Secondary research indicators

- 1) The proportion of people infected with novel coronavirus who turned severe.
- 2) the number of days that novel coronavirus symptoms such as fever, sore throat, headache, and muscle aches persisted in the population infected with neo-coronavirus, and the number of days that the nucleic acid/antigen turned negative.
- 3) The rate of positive serological antibodies in the population of healthy volunteers.
- 4) The incidence of adverse events.
- 5) The difference of T/B lymphocyte specific response to Wuhan Strain and BF.7 Strain in different volunteers.

8.3 Safety indicators

Observation and recording of various adverse events during administration of ursodeoxycholic acid in healthy volunteers

9 Adverse events and serious adverse events

All adverse events, including abnormal clinical symptoms and vital signs, and abnormalities in laboratory tests from the date of signing the informed consent to the last visit were recorded, and the characteristics of clinical manifestations, severity, time of occurrence, duration, management and prognosis were recorded, and their correlation with the trial drug/therapeutic regimen was determined.

Adverse events were graded and recorded with reference to NCI CTCAE 5.0

9.1 Adverse Events

9.1.1 Definition of Adverse Events

Adverse event: An adverse medical event that occurs after a healthy volunteer participates in a clinical study, not necessarily related to the study treatment, and includes any

new event that occurs or worsens in severity and frequency compared to the baseline situation, including abnormal results of laboratory tests, physical examinations, etc. Adverse events include Severe adverse event (SAE), Adverse event (AE), and abnormal laboratory results.

9.1.2 Adverse event collection and recording

Adverse events from the date of signed informed consent to the last visit were recorded, and the investigator applied concise medical terminology to report all possible treatment-related adverse events.

9.1.3 Criteria for determining the severity of adverse events

Use the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to document the severity of adverse events on a scale of 1-5

Grading	Criteria
1	Mild; asymptomatic or mild; seen clinically or diagnostically only; no treatment required
2	Moderate; requires lesser, localized or non-invasive treatment; age-appropriate limitation of instrumental activities of daily living*
3	Severe or medically significant but not immediately life-threatening; resulting in hospitalization or prolonged hospitalization; disabling; limiting personal activities of daily living Δ
4	Life-threatening; requires urgent treatment
5	AE-related deaths

* Instrumental activities of daily living: refers to cooking, buying clothes, using the telephone, managing money, etc.

ΔPersonal activities of daily living: refers to bathing, dressing and undressing, eating, toileting, taking medication, etc., and not bedridden. .

Note:the distinction between severity and intensity of the adverse event. Severity is used to describe intensity and is not necessarily an SAE. e.g. a headache may be severe in intensity but cannot be included in an SAE unless it meets SAE criteria.

9.1.4 Criteria for judging the relationship between adverse events and study drug therapy

The investigators analyzed the relevance of adverse events to the study drug treatment according to the principle of determining the relevance of adverse events to the study drug

treatment, which was divided into 5 categories, namely "definitely related, probably related, probably unrelated, definitely unrelated, and undetermined", and "definitely related, probably related, probably unrelated, and The adverse reactions were classified as "definitely related, probably related, probably unrelated and undetermined". The investigator must document the adverse reactions using medical terminology.

	Is it reasonable Time relationship	Is it consistent with known Type of adverse reaction	Whether there are other reasons forThe possibility of adverse events
Definitely related	Yes	Yes	Yes
Possibly related	Yes	Yes / No	Uncertain
Possibly unrelated	No	No	Uncertain
Definitely not related	No	No	Yes
Unable to judge	Required information for evaluation is not available		

9.2 Serious Adverse Events

9.2.1 Definition of serious adverse events

1. serious adverse event can be defined as any of the following.

1) Deadly or life-threatening.

2) requiring hospitalization or extended hospitalization.

3) Resulting in significant or lasting disability or functional impairment.

4) causing a congenital anomaly or birth defect

5) medically significant and serious illness that endangers the patient's health and requires

medical intervention or surgical intervention to prevent any of the above outcomes.

2. The following admissions are often not considered serious adverse events.

1) Discharge or withdrawal of the patient for progressive exacerbation of the disease requiring hospitalization or extended hospitalization.

2) Hospitalization for routine treatment or observation for indications involved in the trial that are not accompanied by a worsening of the disease;

3) the patient's hospitalization was planned prior to enrollment in this trial and no exacerbation of symptoms that existed prior to the trial was observed

4) Treatment is received only in an emergency, outpatient setting that does not meet any of the above definitions of a serious adverse event and does not require hospitalization.

5) The pregnancy itself is not a serious adverse event, but should be reported on a serious adverse event form or pregnancy record form and should be followed up as well as the outcome documented, including spontaneous abortion or voluntary termination of pregnancy, details of the birth of the infant, and the presence of congenital anomalies and birth defects.

9.2.2 Reporting of serious adverse events

If a Grade 5 serious adverse event occurs in a healthy volunteer during the course of the study (from the date of signing the informed consent to the last visit) and may be related to the study drug treatment, the investigator must complete a serious adverse event report form and report it to the ethics committee of the study center where the event occurred within 24 hours of learning of the event, and the investigator must sign and date the report.

Medical Ethics Committee of the Hospital of Hematology, Chinese Academy of Medical Sciences (Institute of Hematology, Chinese Academy of Medical Sciences)

Contact: Yali Zhang Tel: 022-23909095; E-mail: ec@ihcams.ac.cn

Address: No. 288 Nanjing Road, Tianjin, China

10 Data Management

This study used the Case report form (CRF) for data collection. A dedicated person was developed to enter the contents of the CRF into the database, and a dedicated person verified the consistency of the database with the CRF data. The data manager checked the data in the database according to the clinical study protocol, and if there were any questions, a questionnaire was filled out and the questions in the questionnaire were answered by the investigator.

11 Statistical Methods

11.1 Sample size

The primary endpoint of this study was the rate of novel coronavirus infection in healthy volunteers. The historical novel coronavirus infection rate was estimated to be about 35%, and

the experimental group was expected to control the infection rate at about 20%, taking a two-sided $\alpha=0.05$ with a test efficacy of 90%, and a sample size of 100 cases was calculated using a one-sample rate difference z-test continuity correction method, taking into account the 20% shedding rate and personnel position stratification factors, and 130 healthy volunteers were expected to be enrolled in the final study. The allocation ratios by personnel position were as follows: physicians: 20; nurses: 30; medical technicians: 20; managers: 20; researchers: 20; and medical students: 20.

11.2 Statistical analysis set

Full analysis dataset (FAS): is a dataset determined according to the Intention-To-Treat (ITT) principle and includes all enrolled healthy volunteers who have used the study drug at least once and have at least one analyzable efficacy indicator, and validity analysis is based on the FAS.

Protocol-compliant dataset (PPS): a subset of the overall FAS, including healthy volunteers who did not show significant protocol deviations in the full analysis set, used as an adjunct to the validity analysis.

Safety data set (SS): all healthy volunteers enrolled who received the trial drug and had at least one post-dose safety evaluation data, safety analysis was based on SS.

11.3 Statistical analysis methods

SAS9.4 software was used for statistical analysis of the data in this study, and all tests were performed by two-sided test with test level $\alpha=0.05$ if not otherwise specified.

① Basic methods

The measurement data were described by mean±standard deviation (Mean±SD) or median, maximum, minimum, and interquartile range (Median, Max, Min, IQR); the count data were counted as number of cases and described by rate or percentage; the comparison of measurement data was performed by t test or nonparametric test; the comparison of count data was performed by χ^2 test or Fisher's exact probability test.

② Analysis of primary endpoint indicators

The number and percentage of healthy volunteers with new coronavirus infection were calculated, and 95% exact confidence intervals were calculated using the Clopper-pearson method.

③ Analysis of secondary endpoint indicators

The χ^2 test or Fisher's exact probability test was used to compare the proportion of neo-coronavirus-infected patients in different subgroups who turned to severe disease and the proportion of neo-coronavirus-infected patients without symptoms, and to calculate the confidence interval respectively; the number of days describing the duration of symptoms such as fever and sore throat in infected patients and the number of days to turn negative were calculated; the antibody status of all healthy volunteers and neo-coronavirus-infected patients were described separately.

④ Analysis of safety indicators

The occurrence of adverse events AE and serious adverse events SAE were recorded and described, and the relevance of the events to the study was determined.

⑤ Other analyses

Subgroup and stratified analyses were performed on people of different genders, age groups, staff positions, and staff sections to explore the relationship between the levels of different factors and the effects of neo-coronavirus infection.

12 Ethics Review

12.1 Ethical requirements

This study was conducted in accordance with the current Declaration of Helsinki (2013), relevant regulations and ethics committee review.

Prior to the start of the study, the investigator shall obtain written approval of the study protocol, informed consent form, healthy volunteer recruitment procedures, and other written data to be provided to healthy volunteers from the relevant regulatory unit in accordance with regulations. During the study, if there are any new amendments to the study protocol, informed consent form, etc., written approval from the relevant regulatory authorities should be obtained again in accordance with the regulations

12.2 Informed Consent

The investigator or his/her designated representative will be responsible for explaining to each health volunteer or witness the background of the study, the pharmacological characteristics of the study medical technique, the study protocol, and the benefits and risks of

participation in the study, and shall obtain written informed consent signed by the health volunteer and the study physician prior to the health volunteer's entry into the study (prior to the screening examination).

The final informed consent form should include the following: the purpose of the study, the study procedures, the obligations of the health volunteer, the foreseeable benefits and foreseeable risks and inconveniences to the health volunteer of participating in the study, the availability of treatment for the health volunteer in the event of study-related harm, access to study data, and confidentiality of the health volunteer's information.

The informed consent form should be approved in writing by the relevant regulatory unit in accordance with regulations and written in a language that can be read by the healthy volunteers. The informed consent form should be signed and dated by the health volunteer, the investigator performing the informed consent process, or their representative. One original copy of the informed consent form should be retained by the investigator and one by the healthy volunteer. If important new data concerning the study are discovered, the informed consent form must be revised in writing and sent to the relevant management unit for approval before informed consent is obtained again.

For healthy volunteers who cannot participate in the informed consent process, written informed consent must be obtained from the healthy volunteers and all study procedures, etc., must be explained to the healthy volunteers.

12.3 Confidentiality of information

It is the responsibility of the investigator to maintain the anonymity of the healthy volunteers. Only capital letters, numbers, and/or codes may be used to identify healthy volunteers on case report forms or other documents, not the names of healthy volunteers. The investigator must maintain the healthy volunteer enrollment form that records the healthy volunteer's code, name, and home address. The investigator must maintain strict confidentiality of documents that reveal the identity of the healthy volunteer.

13 Research Management

13.1 Training

Before the start of a clinical study, investigators should receive training on the study protocol, familiarize themselves with and understand the contents of this clinical study protocol, unify the recording methods and judgment criteria, and strictly follow the protocol.

13.2 Quality control and assurance

All observed results and abnormal findings in clinical studies should be carefully verified and recorded in a timely manner to ensure the reliability of the data. The investigator enters the information required by the protocol into the case report form, and the supervisor verifies that it is completed completely and accurately.

14 Confidentiality and publication of research results

The researcher should keep the information and data related to this study confidential, and should not cite or publish the relevant research results or information without the consent of the research unit

15 References

[1] Brevini, T., Maes, M., Webb, G.J. et al. FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2. *Nature* (2022). <https://doi.org/10.1038/s41586-022-05594-0>

16 Annexes

Study Informed Consent Form

Informed Consent Form - Notice Page

Dear Volunteers.

We are planning to conduct a single-center, open, single-arm clinical study of the application of ursodeoxycholic acid for the prevention of novel coronavirus infection at the Hospital of Hematology, Chinese Academy of Medical Sciences (Institute of Hematology, Chinese Academy of Medical Sciences) (hereinafter referred to as "IHCAMS"), and you will participate in this study as a volunteer.

Please read the following carefully so that you can make a decision, which is entirely your own.

I. Background and purpose of the study

In an article titled "FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2" published in Nature on December 5, 2022, ursodeoxycholic acid (UDCA) was found to block novel coronavirus entry into human cells by downregulating angiotensin-converting enzyme 2 (ACE2) expression through inhibition of the transcription factor FXR (from SARS-CoV in 2003 to the SARS-CoV-2 spectrum in 2019 utilized ACE2 as the primary invasion receptor). Because ursodeoxycholic acid acts on the host cell and not on the virus itself, the drug may potentially be able to prevent current novel coronavirus and neo-mutant infections, as well as infections by other coronaviruses that utilize ACE2.

This study was conducted because we are currently in a period of high prevalence of novel coronavirus infections and there is an urgent need to explore therapeutic strategies to prevent neo-coronavirus infections and to prevent further infections in medical personnel.

II. Research Procedures

The study plans to recruit 130 health care workers who are not yet infected with novel coronavirus, including doctors, nurses, technicians, administrators and medical students, aged 18-65 years old, of any gender, and requiring a negative nucleic acid or antigen test for new coronavirus within 48 hours.

After signing the informed consent form, the researcher will collect basic information and perform a routine examination, and collect 8 ml of your blood for storage.

You will then receive ursodeoxycholic acid capsules (250 mg/capsule) for infection prevention, 2 capsules per day for 4 weeks; 8 ml of your blood will be collected and stored at week 4, week 8 or if infection occurs during the study.

You will be followed for 4 weeks after the end of the study, during which time you will be continuously monitored for new nucleic acid/antigen status and antibody testing.◦

III. Possible risks

All drugs and treatments can cause adverse reactions, and there may be risks involved in the research process. Therefore, please be aware of the following details, but not everyone who uses the medication will experience these adverse reactions below.

The main effect of ursodeoxycholic acid is to increase the secretion of bile acids and to cause changes in the composition of bile, lowering cholesterol and cholesterol lipids in bile and facilitating the gradual dissolution of cholesterol in gallstones, which is used clinically for gallbladder cholesterol stones and cholestatic liver disease. Its adverse reactions are mainly diarrhea, the incidence of which is about 2%; occasionally constipation, stomach pain, pancreatitis, headache, dizziness, allergy, bradycardia, etc.; skin may be pruritic, hair loss and the occurrence of bronchitis, cough, pharyngitis and other adverse reactions of the respiratory system.

In addition, some of the known risks associated with blood collection are pain, burning sensation or bruising at the site of blood collection. If you experience any discomfort, or new changes such as infection with a new crown, or any other unexpected situation, whether or not related to this study, please contact the investigator promptly and they will make a judgment and medical treatment for it.◦

IV. Benefits and significance of the study

Participation in this study may prevent you from contracting a novel coronavirus (SARS-CoV-2) or may reduce the symptoms associated with your new coronavirus infection, but it may not have any effect. We hope to use this study to explore treatment strategies to prevent new coronavirus infection.

V. Confidentiality of personal data

IHCAMS will strictly protect the privacy and personal information of volunteers and will adopt the following protection methods: (1) establish confidentiality measures and information security systems, and manage all collected samples anonymously (coding management and/or deletion of all identifying information); (2) store samples and data securely and set access rights to all samples and/or data; (3) samples and

personal information will not be provided to any researchers or institutions outside the Blood Institute; (4) data obtained from research may be published or released publicly, but your name or personally identifiable information will not be released.

VI. Right to make autonomous decisions

You have the right to refuse to participate in the Study, and such refusal will not affect any other rights or interests you may have or affect your normal work. You may withdraw unconditionally at any time

VII. Contact

If during the study you have any complaints or concerns or question your rights as a volunteer, you may contact the following ethics committee staff [Ethics Committee, Hospital of Blood Diseases, Chinese Academy of Medical Sciences, Tel: 022-23909095].

Commitment of the study physician

I, as the study physician, confirm that I have clearly explained to the volunteer the details of this study, that this study is an over-indication of the drug, including its rights as well as possible risks, and have given him/her a signed copy of the informed consent form.

Signature of the study physician: _____

Date of study: _____, _____, _____

Telephone number: _____

Volunteer promise

I have read and understood the relevant information about this study on the informed information page and have had the opportunity to ask questions about it. I understand the researcher's explanations.

I am aware of the risks and benefits that may arise from participating in this study. I understand that participation in the study is voluntary and I acknowledge that I have had sufficient time to consider and voluntarily participate in this study.

I have decided to agree to participate in this study. I will receive a signed and dated copy of the informed consent form.

Volunteer's signature: _____

A single-center, open, single-arm clinical study on the application of ursodeoxycholic acid for the prevention of novel coronavirus infections

_____ Month _____ Year _____ Day _____

Contact number: _____